IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: MOZES2A

In re Application of:	)	Conf. No.: 9655
Edna MOZES et al.	)	Art Unit: 1644
Appln. No.: 10/620,621	)	Examiner: G. R. Ewoldt
Filed: July 17, 2003	)	Washington, D.C.
For: SYNTHETIC PEPTIDES AND PHARMACEUTICAL COMPOSITIONS COMPRISING …	)	January 3, 2008

RESPONSE

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, Mail Stop Amendments
401 Dulany Street
Alexandria, VA 22314

Sir:

The present communication is responsive to the official action of July 10, 2007. Claims 1-15 presently appear in this case. No claims have been allowed. The official action of July 10, 2007, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to the use of certain synthetic peptides for the treatment of systemic lupus erythematosus (SLE). The synthetic peptides are based on a complementarity-determining region (CDR) of the heavy or light chain of a pathogenic anti-DNA monoclonal antibody that induces an SLE-like disease in mice, or a salt or derivative

thereof, as well as dual synthetic peptides and peptide polymers based thereon.

Claims 1-15 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The examiner states that the specification provides insufficient evidence that the claimed method would effectively treat systemic lupus erythematosus (SLE). In response to the evidence that applicant previously cited, the examiner stated that applicant's post-filing references demonstrate encouraging results with the peptides of SEQ ID NO:6 and 8, but such results are not commensurate in scope with the instant claims. This rejection is respectfully traversed.

First of all, it is noted that the examiner concedes that the references employ the peptides that are presently claimed in present claims 7 and 9, i.e., the peptides of SEQ ID NOs:6 and 8. The examiner states, at the top of page 6 of the official action, that applicant's post-filing references demonstrate "encouraging results" with the peptides of SEQ ID NOs:6 and 8, but such results are not commensurate with the scope of the instant claims. It is not understood, however, why the examiner does not consider these results to be commensurate in scope with claims 7 and 9, which claim only peptides of SEQ ID NOs:6 and 8. As this is the only rejection in the case, it is respectfully requested that at least the rejection of claims 7 and 9 be withdrawn and that these claims

be indicated to be allowable. The Sthoeger et al., 2003, paper, of record, establishes that the CDR-based peptides are capable of down-regulating *in vitro* autoreactive T-cell responses of PBL of SLE patients and, thus, these peptides are potential candidates for a novel specific treatment of SLE patients. Such results, in combination with all of the other animal testing that has been conducted with respect to such peptides and reported in the present specification as well as in previously cited post-filing date references, would certainly be sufficient for the FDA to permit clinical trials to commence; that is all that is necessary in order to satisfy the how to use requirement of 35 U.S.C. 112, in accordance with MPEP 2107.03(IV), as cited in applicant's previous response.

Once the proof of concept is established by establishing that the present disclosure is enabling at least for the sequences of claims 7 and 9, it is no longer unreasonable to believe that the remaining peptides within the scope of the present claims will be similarly operable. The examiner states that it is not clear what changes are made to the natural CDRs of the antibody in the "CDR-based peptides", SEQ ID NOs:6 and 8. The answer to this question is readily available to those of ordinary skill in the art as the peptide V_H sequence of the 5G12 antibody is disclosed in the prior art. Submitted herewith is a copy of Waisman et al., "Variable Region Sequences of Autoantibodies from Mice with Experimental Systemic Lupus Erythematosus", *Eur. J. Immunol.*, 23:1566-1573

(1993). It can be seen from Fig 1(B) exactly what is the sequence of the V_H of the 5G12 antibody, including the sequence of CDR1, CDR2 and CDR3, which are enclosed within blocks. SEQ ID NO:6 consists of one amino acid of the sequence before the sequence of the CDR1, the entire sequence of the CDR1 (5 amino acids), and fourteen amino acids downstream of the CDR1. The CDR3-based murine peptide consists of a sequence of five amino acids before the CDR3 sequence, the entire sequence of the CDR3, and five amino acids of the sequence thereafter. It can be seen that the fourth residue of the murine native CDR3 sequence was changed from F to E and the last amino acid is not the one found in the native sequence. These minor changes in the sequence and the decision as to the length of the sequences before and after the CDRs themselves were made taking into consideration the solubility of the peptides, their stability, and certain foreseen problems in the synthesis. Any such minor changes could be readily checked, without undue experimentation, to assure that the modified peptide retains the required inhibitory properties.

Claim 1 does not include any kind of altered peptides. The claimed peptide must include the complimentarity determining region found in the heavy or light chain of a pathogenic anti-DNA monoclonal antibody that induces an SLE-like disease in mice. Claim 6 is directed to specific peptides with very specific possible modifications at certain positions. However, it is clear from the specification that it is the actual CDR that is operable, and

the modifications should be such that the effects of the natural CDR are not substantially changed. In this regard, reference is made to the publications of the inventor, copies of which are submitted herewith, relating to operable analogs of the CDR1 and CDR3 peptides: Eilat et al., "A Peptide Based on the CDR1 of a Pathogenic Anti-DNA Antibody is more Efficient than its Analogs in Inhibiting Autoreactive T Cells", *Immunobiology*, 202:383-393 (2000) and Brosh et al., "A Peptide Based on the Sequence of the CDR3 of a Murine Anti-DNA mAb is a Better Modulator of Experimental SLE than its Single Amino Acid-Substituted Analogs," *Cell Immunol.*, 205:52-61 (2000). Also attached hereto is a press release regarding ongoing clinical trials with respect to a compound in accordance with the present invention: Teva Pharmaceutical Industries Ltd., "TEVA PROVIDES UPDATE ON EDRATIDE FOR SYSTEMIC LUPUS ERYTHEMATOSUS," Teva Press Release, 19 Sept. 2007, <http://www.tevapharm.com/pr/2007/pr_689.asp>.

In any event, it would not take undue experimentation to confirm that each of the peptides claimed does indeed specifically inhibit the proliferative response in cytokine secretion of T-lymphocytes of mice that are high responders to SLE-inducing auto-antibodies. These would then be expected to be operable to the same extent as the mCDR1 and mCDR3 that were tested in the post-filing date references that are of record.

Accordingly, as substantial evidence exists of the operability at least of the peptides of SEQ ID NOs:6 and 8 to

treat SLE in humans, there is insufficient reason to disbelieve the statements of utility in the present specification, at least for those peptides. As these peptides prove the concept, there is no reason to disbelieve the statements in the present specification that the remaining peptides have the same utility. In any event, it would not involve undue experimentation to test each of the others to establish at least the amount of proof that has been provided of record with respect to SEQ ID NOs:6 and 8. Experimentation may be extensive, as long as it is not undue.

Accordingly, reconsideration and withdrawal of this rejection, particularly with respect to claims 7 and 9, and allowance of the claims now present in the case are earnestly solicited.

Respectfully submitted,

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